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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,543	02/12/2004	Harold M. Bates	C015043/0174944	9840

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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,543	BATES, HAROLD M.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12,15-20,22-29,33,34 and 36-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12,15-20,22-29,33,34 and 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/29/10, 4/23/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 3/29/2010, is acknowledged and has been entered. Claims 1 and 22 were amended. Claims 13 and 43-88 were canceled. Accordingly, claims 1-8, 12, 15-20, 22-29, 33-34, and 36-41 are currently pending and subject to examination below in light of the elected species of **OxLDL** as the atherogenic protein and of **C-reactive protein** as the acute phase reactant.

Priority

2. The present application was filed on 2/12/2004. No priority claims have been made.

Objections/ Rejections Withdrawn

3. The objection to the specification has been obviated by Applicant's amendments thereto.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement filed 3/29/2010 and 4/23/2010 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached forms PTO-1449/ PTO/SB/08a.

The first two citations on the IDS of 3/29/2010 have been lined through to avoid duplicate citation on the face of any issuing patent, as the references are already of record (see Applicant's Information Disclosure Statements of 2/12/2004 and 6/23/2004, respectively, which

were previously considered by the examiner as indicated by the signed copies attached to the Office action mailed 11/25/2009).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-8, 12, 15-20, 22-29, 33-34, and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet et al. (U.S. 6,309,888 B1) in view of Valkirs et al. (U.S. 2003/0109420 A1).

Holvoet et al. teach methods for detecting the presence of coronary artery disease by testing samples to determine the level of OxLDL, the level of MDA-modified LDL, and the level of a third marker such as troponin. See especially the abstract; column 1, lines 5-13; column 4, line 1 to column 8, line 45. OxLDL and MDA-modified LDL are atherogenic proteins as defined in the instant specification (page 21, line 22 to page 22, line 5).

Holvoet et al. further teach that OxLDL and MDA-modified LDL can be measured via immunological assays that employ the monoclonal antibodies mAb-4E6, mAB-1H11, or mAb-8A2 (column 4, lines 44-53; column 12, line 29 to column 15, line 33; column 17, lines 39-57; and the claims).

In addition to detecting the presence or absence of coronary artery disease (CAD), the methods of Holvoet et al. can also distinguish between non-acute CAD and acute CAD, where

non-acute CAD means that the patient has either asymptomatic CAD or stable angina (column 3, lines 4-13; column 4, lines 1-15 and line 64 to column 6, line 66). These methods may be conducted as part of a screening or as part of a routine physical examination and may be performed on patients who are **asymptomatic** for coronary artery disease (see especially at column 6, lines 47-66).

It is noted that instant claim 1 recites "detecting whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease" (preamble and step (c)). As discussed above, Holvoet et al. make clear that their methods can be used to diagnose the absence of coronary artery disease, as opposed to the presence of non-acute coronary artery disease (either asymptomatic CAD or stable angina). As such, the methods of Holvoet et al. read on the claimed step of detecting *whether* the patient has asymptomatic CAD since in verifying that CAD is absent, the presence of asymptomatic CAD, stable angina, and acute CAD are being ruled out.

To assess whether marker levels in the patient samples are clinically significant, Holvoet et al. teach the use of predetermined cut points or threshold levels (i.e., cut-points), above which the markers are considered to be indicative of coronary artery disease. See column 4, lines 15-30; column 5, lines 7-63; column 19, lines 15-41; claim 1; and especially at column 8, line 42 to column 10, line 37 and at column 19, lines 33-40.

Holvoet et al. further illustrate measuring levels of C-reactive protein (see column 17, line 64 to column 18, line 2; column 19, lines 15-24; column 21, lines 61-62; column 22, lines 51-53; and Tables III and VI-IX), which is an acute phase reactant as disclosed instantly (specification, page 22, lines 22-23). Holvoet et al. observed that levels of C-reactive protein

were elevated in subjects known to have various types of coronary artery disease as compared with control subjects (see Table III in particular).

Although Holvoet et al. thereby measured levels of the acute phase reactant C-reactive protein, this was apparently done as a means of validating the efficacy of OxLDL and MDA-modified LDL as diagnostic markers, by comparison with other known markers such as C-reactive protein. As explained by Holvoet et al., C-reactive protein was previously known to be a marker of acute coronary syndromes (column 19, lines 15-24).

As such, the teachings of Holvoet et al. differ from the claimed invention in that the reference does not specifically teach using levels of an acute phase reactant as part of their methods to detect the presence, absence, and/or stage of coronary artery disease in a patient.

In addition, with respect to claim 22, Holvoet et al. fail to explicitly teach providing information to a medical professional as recited in the preamble and in steps (c)-(d).

However, it was known in the art at the time of the invention that measuring multiple markers of a disease in a "multimarker" approach may result in improved assay when performing clinical assays.

This is taken to be admitted prior art as Applicant has failed to traverse this assertion. See MPEP 2144.03.

As one example illustrating this common knowledge in the art, Valkirs et al. teach that a plurality of markers can be combined in a "multimarker" strategy to increase the predictive value of an analysis (diagnostic or prognostic) in comparison to that obtained using the markers individually [0017], [0107], [0184].

Valkirs et al. also teaches that C-reactive protein can be used not only for identifying individuals who already have acute coronary syndrome, but also for identifying individuals who are at risk for later developing acute coronary syndrome ([0090], [0191]).

Therefore, because OxLDL, MDA-modified LDL, and C-reactive protein were all recognized by Holvoet et al. to be markers correlated with the presence and/or stage of coronary artery disease, it would have been obvious to one of ordinary skill in the art to also measure C-reactive protein levels and to use this information when detecting whether an asymptomatic patient has coronary artery disease according to the methods of Holvoet et al. In particular, it would have been obvious to also measure levels of C-reactive protein in asymptomatic subjects and to compare the observed levels with predetermined cut points or threshold levels in the same manner taught by Holvoet et al. for OxLDL and MDA-modified LDL, so as to assess the presence, absence, and/or stage of asymptomatic coronary artery disease in the patient. Put another way, when detecting C-reactive protein in addition to OxLDL and MDA-modified LDL as part of the multimarker strategy of Valkirs et al., it would have been obvious to employ cut points for each marker being assayed (e.g., a first cut-point for OxLDL, a second cut-point for C-reactive protein, etc.) and to compare the subject's observed marker levels with these predetermined levels in the same manner illustrated by Holvoet et al. for their multimarker assay, in order to properly interpret the results of the assay.

One would be motivated to combine the reference teachings in this manner in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually.

With respect to the steps of "providing information to a medical professional" as in claim 22, it is noted that Holvoet et al. discuss how their methods, which use multiple tests together, rapidly provide all the information needed by the clinician about the patient to permit possible life-saving treatment (column 6, line 48 to column 7, line 4; column 10, lines 38-63). The reference further discusses how a physician would use the results of the methods for diagnosis and treatment (ibid). For example, when the methods indicate that the patient has non-acute coronary artery disease, the physician may take action such as recommending a change in life style, prescribing appropriate medication, etc. (column 6, lines 48-66).

Therefore, although Holvoet et al. do not explicitly disclose a step in which the results of the method are provided to a medical professional to then use in determining whether the individual has coronary artery disease, the reference nonetheless clearly conveys that the results of their methods can be used by a physician in order to diagnose the presence, absence, and/or stage of coronary artery disease; as well as to administer appropriate treatment. When taken together with the general knowledge in the art, therefore, it would have been obvious to one of ordinary skill in the art to provide the results of the method of Holvoet et al. and Valkirs et al. to a physician so that the patient could be diagnosed and appropriately treated. For example, it would have been obvious to conduct the method in a clinical laboratory setting and to communicate the patient's test results to their physician in accordance with routine medical care practices.

With respect to claims 3, 18, 24, and 39, Holvoet et al. teaches detection of OxLDL whose apo B-100 moieties contain at least 60 substituted lysine residues (column 12, lines 55-65).

With respect to claims 6, 8, 15, 17, 19, 27, 29, 36, 38, and 40, which refer to detection of HDL as an anti-atherogenic protein, it is noted that Holvoet et al. also measured levels of HDL cholesterol (column 17, line 58 to column 18, line 6; and Tables III and V-IX). As such, it would have been further obvious to one of ordinary skill in the art to also measure HDL levels when performing the methods of Holvoet et al. and Valkirs et al., since the teachings of Holvoet et al. indicate that HDL is a marker that is normally measured when assessing coronary artery disease. In addition, it is noted that the data of Holvoet et al. demonstrate that HDL levels are correlated with the presence of coronary artery disease (Table III and column 20, lines 28-67). When taken together with the teachings of Valkirs et al. as discussed above, it would also have been obvious to measure HDL in addition to the markers discussed above when assessing subjects for the presence, absence, and/or stage of coronary artery disease. As above, one would be motivated to do this in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually.

Response to Arguments

3. With respect to the rejections of Claims 1-8, 12, 15-20, 22-29, 33-34, and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet et al. (U.S. 6,309,888 B1) in view of Valkirs et al. (U.S. 2003/0109420 A1), Applicant's arguments filed 3/29/2010 (see pages 16-37) have been fully considered but they are not persuasive.

Applicant argues that the rejection did not explain *why* one skilled in the art would modify Holvoet or Valkirs to arrive at the claimed process (Reply, page 24, first full paragraph).

This is not found persuasive because as discussed in the rejection of record, measuring multiple markers of a disease in a "multimarker" approach was known to improve assay performance (see above and the previous Office action at pages 6-7). As such, it is maintained for reasons of record that one would be motivated to also use C-reactive protein levels in the method of Holvoet et al. because the inclusion of additional markers of disease would be expected to improve assay performance.

Applicant further asserts that one skilled in the art would not have reasonably expected success in combining the teachings of Holvoet and Valkirs as claimed (Reply, pages 24-26).

This is not found persuasive because the claimed invention relates to a method of detecting whether a patient has asymptomatic coronary artery disease, as distinguished from patients who do not have disease.

As discussed in detail above, Holvoet et al. indicate that detecting OxLDL and MDA-modified LDL would be sufficient to accomplish this goal. Moreover, it was common knowledge in the art (as taught for example by Valkirs et al.) that measuring multiple markers of disease may result in improved assay performance. As such, when adding the additional marker C-reactive protein, it is maintained that one of ordinary skill in the art would have had a reasonable expectation of success in detecting asymptomatic CAD as claimed, since even without C-reactive protein this discrimination is possible according to the methods of Holvoet et al.

Similarly, in regards to Applicant's arguments that Holvoet et al. does not suggest, provide motivation, or any expectation of success in the use of an acute phase reactant (such as CRP) in achieving discrimination between individuals with CAD from those without CAD (Reply, page 28), it is emphasized that the claimed invention involves detecting both OxLDL and

C-reactive protein. Since detection of OxLDL or MDA-modified LDL alone are sufficient to detect asymptomatic CAD, one would have had a reasonable expectation of success when even more markers were included.

Applicant further argues that Holvoet does not suggest, provide motivation, or provide any expectation of success in detecting "with significant discrimination" whether the patient has asymptomatic CAD as distinguished from those who do not have CAD. Applicant argues that Holvoet does not suggest that markers could "significantly" distinguish between patients with no CAD and those with asymptomatic CAD, all of whom are asymptomatic. See Reply, page, last paragraph to page 27, first paragraph; the paragraph bridging pages 29-30; and the paragraph bridging pages 35-36.

As best understood, Applicant acknowledges that Holvoet teaches detection and discrimination of asymptomatic CAD as distinguished from those who do not have CAD, but argues that Holvoet does not teach “significant” discrimination.

In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., that Holvoet does not teach “significant discrimination” of asymptomatic CAD) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims do not require any particular level of accuracy in regards to the discrimination of asymptomatic CAD.

Furthermore, in light of the common knowledge in the art as well as the teachings of Valkirs et al., the inclusion of C-reactive protein as an additional known coronary marker would have been *expected* to result in improved assay performance.

Applicant further argues that Holvoet does not consider C-reactive protein in terms of distinguishing individuals without CAD from those with CAD, but rather teaches this protein as a marker of inflammation and of acute coronary syndromes (Reply, pages 27-28). Applicant argues that Holvoet et al. does not suggest, provide motivation, or any expectation of success in the use of an acute phase reactant (such as CRP) in achieving discrimination between individuals with CAD from those without CAD (Reply, page 28).

This is not found persuasive because as discussed above, the claimed invention involves detecting both OxLDL and C-reactive protein. Since Holvoet et al. indicate that detection of OxLDL and MDA-modified LDL alone are sufficient to detect asymptomatic CAD, one would have had a reasonable expectation of success when even more markers were included.

Moreover, although the teachings of Holvoet et al. in regards to asymptomatic CAD are most relevant to the claimed invention, the reference also contemplates detecting acute coronary disease. As such, even if Applicant's arguments may be adopted that C-reactive protein is only taught as a marker of acute coronary syndrome, it would still have been obvious to incorporate C-reactive protein into the multimarker methods of Holvoet et al. since it these methods are designed not only for asymptomatic patients, but also for those who may have acute coronary syndrome.

For all of these reasons, it is maintained that a determination of obviousness does not require that Holvoet explicitly teach C-reactive protein as a marker for asymptomatic CAD.

Notwithstanding the above, the record reflects that such a nexus was indeed recognized in the art at the time of the invention.

In particular, as discussed above Valkirs et al. teach that activation of markers associated with inflammation and the acute phase response, including C-reactive protein, can be used not only to identify risk of later development of disease [0090].

See also Ridker et al. (Circulation. 1998 May 26;97(20):2007-11; Applicant's Information Disclosure Statement of 2/12/2004), who provide evidence that CRP was known to be a marker of cardiovascular risk even among individuals with no current evidence of disease (page 2007, left column).

Similarly, Ridker et al. (Circulation. 1998 Aug 25;98(8):731-3; Applicant's Information Disclosure Statement of 2/12/2004) taught that CRP has clinical utility as a marker for vascular disease even in apparently healthy women (see title, abstract, and page 733, left column).

Hirschfield et al. (QJM. 2003 Nov;96(11):793-807; Applicant's Information Disclosure Statement of 2/12/2004) provide evidence that CRP was suggested in the prior art to contribute to the pathogenesis, progressions, and complications of atheroma and atherosclerosis (see the paragraph bridging the left and right columns of page 798; and also at page 800). Consequently, elevation of CRP in the early stages of atherosclerosis (i.e., before the symptomatic period) would have been reasonably expected if this molecule was known to play a part in the pathogenesis of disease.

Solely to address Applicant's remarks, it is noted that many other references recognized this link between C-reactive protein and coronary artery disease, even at the asymptomatic stage.

Zimmerman et al. ("Diagnostic Implications of C-Reactive Protein" ARCH SURG/VOL 138, FEB 2003, 220-224), teach that levels of circulating CRP may identify otherwise asymptomatic patients who are at sufficient cardiovascular risk to warrant aggressive therapy (abstract).

Redberg et al. ("Lack of Association of C-Reactive Protein and Coronary Calcium by Electron Beam Computed Tomography in Postmenopausal Women: Implications for Coronary Artery Disease Screening" Journal of the American College of Cardiology, Vol. 36, No. 1, 2000, pages 39-43), provide further evidence that CRP was thought to be a molecular marker of preclinical (i.e., asymptomatic) atherosclerosis (see page 39, right column).

Indeed, the link between C-reactive protein and cardiovascular events even in apparently healthy individuals had been reported even in the popular press prior to Applicant's invention (see New York Times Article entitled "Hunt for Heart Disease Tracks a New Suspect", January 6, 2004; Applicant's Information Disclosure Statement of 2/12/2004).

Applicant's arguments that Holvoet does not teach C-reactive protein as a marker of asymptomatic CAD therefore fail to take into account the abundant knowledge in the art regarding this protein. Given the well recognized utility of C-reactive protein as the marker even in early stage coronary disease, the evidence of record indicates that one of ordinary skill in the art would have reasonably expected inclusion of C-reactive protein measurements to add further clinical information regarding detection of asymptomatic CAD.

Applicant further argues that the third marker used by Holvoet et al. is a "heart protein" and not an acute-phase reactant. Applicant argues that acute-phase reactants are not specific but can occur in diseased or non-diseased individuals. See Reply, pages 29-30.

As best understood, Applicant argues that one of ordinary skill in the art would not have been motivated to include C-reactive protein because it is not specific to disease.

This is not found persuasive because it was recognized in the prior art that even non-specific markers can be useful in diagnosis when used as part of a panel of markers (Valkirs et al., abstract).

Applicant also focuses on the particular details of Valkirs et al, arguing that the reference is directed to acute coronary syndrome and not to asymptomatic disease. See Reply, pages 30-31.

This is not found persuasive because the noted teaching is found in the primary reference. Moreover, as discussed above, Valkirs et al. also contemplates prognosis of acute coronary syndrome, i.e. assessing risk of later development of disease. As such, the reference also contemplates early stage coronary disease.

Applicant further argues that Valkirs et al. associates C-reactive protein with the acute phase of CAD, and therefore teaches away from its use in the claimed methods which are directed to asymptomatic CAD (Reply, pages 30-32).

This is not found persuasive because initially, the fact that a marker is correlated with symptomatic disease does not necessarily mean that it is *not* correlated with early stage, asymptomatic disease. Furthermore, as discussed above, Valkirs et al. indicate that C-reactive protein can be used not only to diagnose acute coronary syndrome, but also to identify those individuals at risk for later development of acute coronary syndrome (i.e., those who do not yet have full-blown disease). As such, the reference also positively correlates C-reactive protein with early stage coronary disease.

In addition, a reference "teaches away" if a person of ordinary skill in the art would have been discouraged or led to a divergent path from the one taken by the inventors. In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

Here, rather than discourage, Valkirs et al. simply do not mention C-reactive protein in the context of asymptomatic coronary disease; but as noted above, the reference does indicate that this protein may be elevated even in the early stages of disease, in individuals who do not yet have acute coronary syndrome.

Similarly, Applicant's arguments that Valkirs et al. teaches away from the claimed invention in discussing the normal variability in CRP levels (Reply, pages 31-32) does not rise to the level of a teaching away as the reference teaches, rather than disparages, the use of CRP as a marker.

Applicant's arguments that Valkirs does not teach or suggest the use of cut-points (Reply, pages 32-34) are not persuasive because the noted teachings are found in the primary reference.

Applicant also points to a marketing brochure purported to describe the advantages of the commercially available Oxidized LDL Triple Marker Test. Applicant states that the brochure "indicates advantageous results". See pages 34-36.

As best understood, Applicant argues for the presence of secondary considerations, namely unexpected results.

Whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007).

As such, the burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an unexpected difference." In re Klosak, 455 F.2d 1077, 1080 (CCPA 1972). Moreover, it has been long held that "even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges 'produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." In re Huang, 100 F.3d 135, 139 (Fed. Cir. 1996) (quoting In re Aller, 220 F.2d 454, 456 (1955), and citing In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990)).

In the instant case, Applicant has not contended that the advantageous results are "unexpected". In light of the common knowledge in the art that a "multimarker" strategy was commonly known to provide improved clinical assay performance over individual markers alone (a concept taught for example by Valkirs et al.), the evidence of record indicates that inclusion of

C-reactive protein as an additional marker in the methods of Holvoet et al. would have been *expected* to be associated with advantageous results.

In addition, no comparison to the closest prior art has been made; nor are the asserted advantageous results commensurate with the scope of the claims.

For all of these reasons, the arguments of counsel and the indicated marketing brochure do not constitute sufficient evidence to establish the presence of unexpected results.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Reply, page 36-37), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641
6/29/10